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PATENT SPECIFICATION

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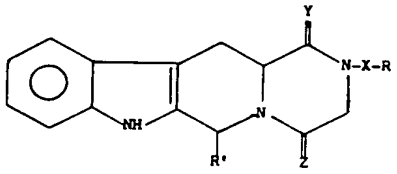
C2C 1360 136X 1530 1693 213 214 215 220 226 22Y 246 247 248 250 251 252 253 258 25Y 28X 304 305 30Y 311 313 314 31Y 323 326 32Y 338 339 350 351 352 355 35Y 360 361 362 363 364 366 367 368 36Y 37X 386 387 388 43X 490 502 503 509 50Y 54X 620 623 624 625 628 62Y 635 650 652 655 656 658 65X 662 665 675 678 697 69Y 73Y 761 762 770 776 778 77X 790 79Y BC LK NL NS TA TR UH UL WC ZD ZF

(54) TETRACYCLIC COMPOUNDS

(71) We, COUNCIL OF SCIENTIFIC & INDUSTRIAL RESEARCH of Rafi Marg, New Delhi, Delhi, India, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with novel pharmacologically active substances. More particularly, this invention relates to 2 - substituted - 1,2,3,4,6,7,12,12a - octahydropyrazino[1′,2′:1,6]pyrido[3,4-d]indoles of the formula



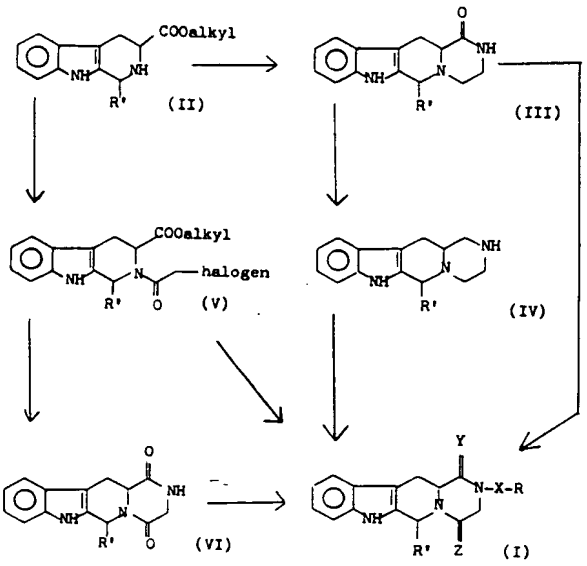
wherein X is a straight or branched alkylene, oxoalkylene or hydroxyalkylene chain; R is hydrogen, lower alkyl, aryl, aryloxy, cyano, carboxy, carbalkoxy, dialkylamino, benzodioxanyl or 4-pyridyl, or XR is hydrogen; R¹ is hydrogen or lower alkyl; Y and Z independently represent H_2 or an oxygen atom, with the proviso that when Y represents H_2, Z does not represent an oxygen atom; and pharmaceutically acceptable acid addition and quaternary ammonium salts thereof.

In the specification, the term " straight or branched alkylene, oxoalkylene or hydroxyalkylene chain " designates chains containing from 1 to 6 carbon atoms, such as ethylene, propylene, butylene or amylene, in which one of the methylene groups may be replaced by a carbonyl or a hydroxymethylene group, such as CH_2CH_2CO, $CH_2CH_2CH_2CHOH$, CH_2CO or CH_2CH_2CHOH. The term " lower alkyl " designates alkyl groups which are straight or branched and contain 1 to 6 carbon atoms. " Aryl " designates a phenyl group or a phenyl group substituted by one or more alkyl, alkoxy or halogen groups. " Aryloxy " generally designates phenoxy or a substituted phenyl group.

A preferred group of compounds comprises those in which X is a carbon chain of 2—4 members in which a CO or a CHOH group is present, and R is a lower alkyl group or a phenyl group, the latter being unsubstituted or substituted with a fluorine atom or a lower alkoxy group. Preferably, these compounds do not bear oxygen functions at positions 1 and 4, in other words the radical Y and Z both represent H_2.

The compounds of this invention have useful biological activity, and have in particular strong tranquillizing and hypotensive activity. Accordingly, the present invention provides pharmaceutical compositions comprising a compound of the invention in association with a pharmaceutically acceptable diluent or carrier.

The general reaction sequence leading to the compounds of the invention is given below:



It will be noted that, in the above reaction scheme, there are two general methods leading to the synthesis of I. In both methods the starting material is an alkyl 1,2,3,4-tetrahydro - 9H - pyrido[3,4-b]indole - 3 - carboxylate II, prepared by the condensation of tryptophan with different aldehydes by known methods.

By the first general method, the alkyl 1,2,3,4 - tetrahydro - 9H - pyrido-[3,4-b]indole - 3 - carboxylate is condensed with ethyleneimine in a polar solvent such as methanol, ethanol or butanol, preferably in the presence of an acid catalyst such as hydrochloric acid, and desirably at the boiling point of the solvent to give 1 - oxo-1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido[3,4-b]indoles of formula III. If compounds of formula I in which Y and Z are both H_2 are desired as the end compound, lithium aluminium hydride reduction of III in a nonpolar aprotic solvent such as ether, diglyme, tetrahydrofuran or dioxane at temperatures varying from 40° to 100°C gvies 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido[3,4-b]indoles (IV). Substituents are then introduced at the 2-position of III or IV by a variety of methods.

By way of example, reaction of compounds of formula IV with a reagent of the structure R—X—halogen (where R and X are as defined above and halogen is either chlorine or bromine) gives 2 - substituted - 1,2,3,4,6,7,12,12a - octahydropyrazino-[1',2':1,6]pyrido[3,4-b]indoles (I, where Y and Z are both H_2). This reaction is carried out in a solvent such as acetone, methyl ethyl ketone, tetrahydrofuran or dimethylformamide, using a base such as triethylamine, pyridine or sodium or potassium carbonate. Sodium iodide can be optionally included in the reaction mixture to improve the yields of I. When amides of formula I are obtained, in which a carbonyl group is linked to the nitrogen atom at position 2, and Y and Z are H_2, on lithium aluminium hydride reduction in a solvent such as ether, tetrahydrofuran or diglyme at a temperature of up to the boiling point of the solvent, compounds of formula I are obtained, where R and R' are as defined above; X is alkylene; and Y and Z are H_2. The amides in which a carbonyl is bound to the nitrogen atom at position 2 can also be obtained by the reaction of compounds of formula IV with an excess of an alkyl alkanoate (RCOO alkyl) at the boiling point of the reagent.

By the second method, alkyl 1,2,3,4 - tetrahydro - 9(H)pyrido[3,4-b]indole-3 - carboxylates (II) are reacted with a haloacetyl halide to give alkyl 2 - haloacetyl-1,2,3,4 - tetrahydro - 9H - pyrido[3,4-b]indole - 3 - carboxylates (V). This reaction is best carried out by adding equimolecular amounts of chloroacetyl chloride in an aprotic solvent such as chloroform, benzene, toluene or ether and at a temperature up to the boiling point of the solvent

The compounds of formula V, obtained by the above method, are condensed with primary amines of the structure H_2N—X—R (where R and X are as defined above) in an alcoholic solvent such as ethoxy ethanol and at a temperature varying from 100—130° to give 2-substituted 1,4 - dioxo - 1,2,3,4,6,7,12,12a - octahydropyrazino-

[2',1':6,1]pyrido[3,4-b]indoles of formula where Y and Z are oxygen.

If ammonia is used instead of a primary amine, the compound above is obtained, into which substituents at position 2 can be introduced, if desired after hydrogenation of the two oxo groups according to the procedure already indicated for preparing compounds of formula I from compounds of formulae III and IV.

2 - Substituted - 1,3,3,4,6,7,12,12a - octahydropyrazino[2',1':6, pyrido[3,4-b]-indoles (I) in free base form can, if desired, be converted into their non-toxic pharmaceutically acceptable acid addition and quaternary ammonium salts. Salts which may be formed comprise, for example, salts with inorganic acids, such as hydrochloride, hydrobromide, hydroiodide, sulfate or phosphate salts. They may also comprise salts with organic acids including monobasic acids such as the acetate or propionate and especially those with hydroxy organic acids and dibasic acids, such as the citrate, tartrate, malate or maleate salts. Among the useful quaternary ammonium salts are those formed by such alkyl halides as methyl iodide and n-hexyl bromide.

It will be apparent to all those skilled in the art that if racemic tryptophan is used for preparing the starting compound II, the end compound I will also be a racemate, like all other intermediates prepared in the course of the synthesis. On the contrary, if natural L-tryptophan is used, a subsequent intermediates as well as the end compounds may retain the steric configuration and be present in the form of the L-isomer. In fact, the synthesis of compound IV above is stereospecific, since starting from L-tryptophan the optically active compound of formula III is obtained, and the tetracyclic base IV derived from III is also optically active. The chiral centre 12a is L—III and in L—IV has S-configuration as present in L-tryptophan.

The compounds of the invention show a marked depressant activity, as shown, for instance, by the following pharmacological data, obtained by subjecting to animal tests the compound 2 - γ - (p - fluorobenzoylpropyl) - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido[3,4-b]indole.

Acute Toxicity

a) *Mice* LD_{50} 180 mg/kg i.p.
>1 G/kg p.o.

b) *Rat* LD_{50} 700 mg/kg p.o.

Gross Effects: Sedation, reduced spontaneous motor activity, eye closure at 2.5—35 mg/kg i.p. doses in mice. There is however no marked hypothermia at these dose levels.

C.N.S. Effects Were tested in groups of 5 animals each unless indicated otherwise. All tests were done 1 hour after drug administration.

a) *Amphetamine hyperactivity test (mice)* ED_{50} 0.5 mg/kg i.p.

b) *Amphetamine toxicity test in mice* ED_{50} 2.9 mg/kg i.p.

c) *Effect on conditioned avoidance response in rate* ED_{50} 0.16 mg/kg i.p.
0.25 mg/kg p.o.

d) *Rotard test (mice)* ED_{50} 5.9 mg/kg i.p.

e) *Effect on pentobarbitone sleeping time (mice)*: 100 percent prolongation in sleeping time at 0.5 mg/kg i.p.

f) *Effect in monkey*:

i. *Intraperitoneal*: Doses of 0.6, 0.9, 1.25 and 2.5 mg/kg i.p. were given in groups of 4 aggressive monkeys each. The compound exhibited progressive C.N.S. depression with increasing doses manifested by quietness, reduction in aggressiveness, animal sitting in one corner of the cage and ptosis. The effect started between 2—4 hours and lasted about 48 hours.

ii. *Oral* Doses of 0.25, 0.5 and 1.5 mg/kg were administered in groups each of 4 monkeys and 1, 2.5 and 5 mg/kg in groups of 2 monkeys each. At doses of 0.25—2.5 mg/kg there was quietness, sedation, ptosis and reduced aggressivness. There was no catalepsy and the animals were eating well. At 5 mg/kg there was in addition catalepsy and reduced food intake. The effects came about 2 hours after drug administration and persisted for about 48 hours.

g) *Effects in cat*: Doses of 1, 2 and 5 mg/kg given in 2 cats each produced signs of C.N. depression e.g. sedation, ptosis and reduction in aggression. The effects appeared after 10 hours and lasted 24 hours.

h) *Antiemetic activity* Was studide in dogs in groups of 4 each. Emesis was induced by intravenous injection of apomorphine 50 μg/kg. The compound produced 100% protection up to a dose of 125 μg/kg i.p.

i) *E.E.G.* A dose of 2 mg/kg i.v. in cat produced abolition of reticular arousal.

j) *Anticonvulsant activity* The compound did not afford protection against seizures induced by supra maximal electroshock (48 mA × 0.2 sec) metrazol 80 mg/kg subcutaneously or strychnine 1.5 mg/kg i.p. in mice.

k) *Antireserpine activity (mice)* The compound was devoid of MAO inhibitor activity at 30 mg/kg i.p.

Cardiovascular effects (cat)

Cats were anesthetised with pentobarbitone (30 mg/kg i.p.). The compound produced no significant effect on blood pressure or respiration at doses ranging from 1 to 10 mg/kg i.v. The pressor responses to noradrenaline and carotid occlusion were also not modified.

Isolated guinea pig ileum

There was no effect up to a concentration of 5×10^{-3} mg/ml. Higher concentrations antagonised histamine induced contractions.

Comparable pharmacological results were obtained with a number of other compounds of the class.

The following are examples of preparation of the compounds of the invention.

Example 1.

1 - Oxo - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido[3,4-b]indole.

Ethyleneimine (2.5 ml) is added to a solution of methyl - 1,2,3,4 - tetrahydro-9H - pyrido[3,4-b]indole - 3 - carboxylate (12.4 g) and the hydrochloride salt of the latter (0.0124 in absolute ethanol (125 ml) and refluxed for 24 hr. Then another aliquot of ethylene imine (2.5 ml) is added and reflux continued for another 24 hr. Concentration of the reaction mixture gives the product, which is recrystallized from absolute ethanol, yield 8.0 g, m.p. 260—261°C.

Example 2.

1,2,3,4,6,7,12,12a - Octahydropyrazino[1',2':1,6]pyrido[3,4-b]indole.

A mixture of 1 - oxo - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido[3,4-b]indole (6.0 g), lithium aluminium hydride (12.0 g) in tetrahydrofuran (450 ml) is refluxed for 48 hr, cooled and the complex decomposed by successive addition of water, 10% sodium hydroxide solution and water, filtered and the filtrate concentrated to give the product, yield 4.2 g., m.p. 230—232°C.

Example 3.

2 - γ - (p - Fluorobenzoylpropyl) - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]-pyrido[3,4-b]indole.

A mixture of 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido[3,4-b]-indole (2 g), γ - chloro - p - fluorobutyrophenone (2.54 g), anhydrous sodium carbonate (0.94 g) and dry sodium iodide (0.48 g) in dry dimethylformamide (40 ml) is stirred at 80°C for 36 hr. The reaction mixture is diluted with water (100 ml) and extracted with benzene. The benzene extract is dried on anhydrous sodium sulfate, evaporated and the residue crystallized from benzene-hexane to give the product, yield 2.2. g, m.p. 188—189°C.

Example 4.

2 - β - Diethylaminoethyl - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido-[3,4-b]indole.

Obtained by a similar procedure as described in Example 3, m.p. 98—99°C.

Example 5.

2 - Methyl - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido[3,4-b]indole.

A mixture of 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido[3,4-b]-indole (2.25 g) and ethyl formate (15 ml) is refluxed for 60 hr. The reaction mixture is evaporated and the residue crystallized from benzene-hexane to give 2 - formyl-1,2,3,4,6,7,12,12a - octahydropydazino[1',2':1,6]pyrido[3,4-b]indole. Yield 2.2 g, m.p. 118,121°C. The obtained formyl compound (1.3 g) in dry tetrahydrofuran (10 ml) is added under stirring to lithium aluminium hydride (1.5 g) in tetrahydrofuran (20 ml). The reaction mixture is stirred and refluxed for 24 hr. and worked up as described in example 2 to give the product. Yield 0.85 g. m.p. 227—229°C.

Example 6.

2 - Phenylacetyl - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido[3,4-b]-indole.

Phenylacetyl chloride (0.53 ml) in dimethylformamide (5 ml) is added under stirring to a solution of 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido-[3,4-b]indole (1.14 g) and dry pyridine (0.6 ml) in dimethyl formamide (25 ml). The reaction mixture is stirred for 24 hr. and diluted with water, when the product separated as an oil and slowly crystallised on keeping for 12 hr. at 25°C, yield 0.8 g, m.p. 198—200°C.

Example 7.

2 - Phenethyl - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido[3,4-b]indole.

The above phenylacetyl compound is reduced with lithium aluminium hydride in tetrahydrofuran by the method described in example 2, to give the product, yield 0.5 g, m.p. 207—208°C.

Example 8.

2 - β - Diethylaminoethyl - 1,4 - dioxo - 1,2,3,4,6,7,12,12a - octahydropyrazino-[1',2':1,6]pyrido[3,4-b]indole.

A solution of chloroacetyl chloride (1.5 ml) in chloroform (10 ml) is added over about 40 minutes to a solution of methyl 1,2,3,4 - tetrahydro - 9H - pyrido[3,4-b]-indole - 3 - carboxylate in dry chloroform (20 ml) under stirring. The reaction mixture is stirred and refluxed for 6 hours. Methanol (2 ml) is added, the solvent is evaporated in vacuum and the residue crystallized from benzene-heptane to give methyl 2 - chloroacetyl - 1,2,3,4 - tetrahydro - 9H - pyrido[3,4-b]indole - 3 - carboxylate. Yield 0.92 g, m.p. 175—176°C. A solution of the obtained ester (0.81 g), β - diethylaminoethylamine (0.37 g) in dry Cellosolve (20 ml) is refluxed for 13 hrs. (" Cellosolve " is a registered Trade Mark). The solvent is removed *in vacuo* and the residue chromatographed on silica gel in chloroform. Elution with chloroform gives the title compound which recrystallizes from chloroform-ethyl ether, yield 0.46 g., m.p. 143—145°C.

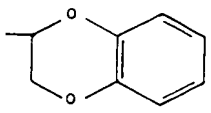
Example 9.

2 - β[4 - Pyridyl] - ethyl - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido-[3,4-b]indole.

A solution of 11.55 g. of 4-vinylpyridine, 6 g. of acetic acid and 22.7 g. of 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido[3,4-b]indole in 1500 ml. of ethanol is refluxed for 20 hrs., then the reaction mixture is evaporated to dryness. The residue is taken in water (200 ml.) and made alkaline with 2N NaOH to give the title compound.

Examples 10 to 18.

By substantially the same process as in example 3 the following compounds of the generic formula I in which Y and Z are both H_2 and R' is H are prepared:

Example	X	R	m.p. (°C)
10	CH_2CH_2CO	C_6H_4F-p	215–216
11	CH_2CO	C_6H_4F-p	235
12	$CH_2CH_2CH_2CH_2CO$	C_6H_4F-p	150–151
13	$CH_2CH_2CH_2CH_2CO$	C_6H_5	144–146
14	$CH_2CH_2CH_2CO$	C_6H_5	165–166
15	$CH_2CH_2CH_2CO$	C_6H_4Br-p	200
16	$CH_2CH_2CH_2CO$	$C_6H_4OCH_3-p$	161–163
17	$CH_2CH_2CH_2CO$	$C_6H_4CH_3-p$	176
18	CH_2		118

Example 19.

2 - [2 - Phenyl - 2 - hydroxyethyl] - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]-pyrido[3,4-b]indole.

A mixture of 2.27 g of the compound of example 2 and 1.44 g of 1-phenylethylene epoxide in anhydrous ethanol is refluxed for 12 hrs. The reaction mixture is then evaporated to dryness giving the product. M.p. 223°C (from ethanol).

Example 20.

2 - (2 - Phenoxy - 2 - hydroxyethyl) - 1,2,3,4,6,7,12,12a - octahydropyrazino-[1',2':1,6]pyrido[3,4-b]indole.

Prepared by the same procedure as in Example 19. M.p. 180—182°C (from ethanol).

Example 21.

2 - [4 - (p - Fluorophenyl) - 4 - hydroxy - butyl] - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido[3,4-b]indole.

To a stirred solution of 11 g. of the compound of Example 3 in 500 ml of methanol, 0.75 g. of $NaBH_4$ were added slowly, and stirring was continued for 14 hrs. at 30°C. The reaction mixture was evaporated to dryness and the residue was triturated with water to give the title compound, m.p. 138—140°C (from ethanol).

Example 22.

2 - (3 - Hydroxybutyl) - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido-[3,4-b]indole.

Prepared by the same method as in Example 21. The m.p. is 193°C.

Examples 23 to 25.

2 - (3 - Oxobutyl) - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido[3,4-b]-indole.

To a stirred solution of the compound of Example 2 (2.27 g) in anhydrous dimethylformamide (500 ml.), 0.7 g. of methyl vinyl ketone were added, and stirring was continued for 24 hrs. at 30°C. The reaction mixture was poured into water and the product recovered by filtration (M.p. 141°C). By exactly the same process, but using as starting compounds ethyl vinyl ketone and butyl vinyl ketone, the analogues having at position 2 a 5-membered and a 7-membered carbon chain were prepared. The melting points are respectively 161°C and 137°C.

Example 26.

2 - (2 - Cyanoethyl) - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido[3,4-b]-indole.

A mixture of the compound of Example 2 and a large excess of acrylonitrile is refluxed for 30 hrs and then it is cooled giving the desired product; m.p. 206°.

Example 27.

2 - (2 - Carbethoxyethyl) - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido-[3,4-b]indole.

Prepared like the compound of Example 26, using ethyl acrylate instead of acrylonitrile, m.pt. 125°C. When hydrolyzed with NaOH in water/ethanol the compound gives the free carboxylic acid; m.p. 235°C.

Example 28.

2 - (3 - Phenyl - 3 - hydroxy)butyl - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]-pyrido[3,4-b]indole.

Prepared via a Grignard reaction from the compound of Example 23 and phenylmagnesium bromide; m.p. 164°C (from ethyl acetate).

Example 29.

2 - (3 - Hydroxypropyl) - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido-[3,4-b]indole.

A solution of 3.27 g. of the compound of Example 27 in 200 ml. of tetrahydrofuran is added to a stirred suspension of 1.52 g. of $LiAlH_4$ in 50 ml of ethyl ether. The reaction mixture is heated at 50—55°C for 4 hrs. and then worked up as usual in this kind of hydrogenation; m.p. 165°C.

Example 30.

cis - 1 - Oxo - 6 - methyl - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido-[3,4-b]indole.

Ethyleneimine (5.6 ml) in 400 ml of anhydrous ethanol is added slowly to a stirred and refluxing solution of a mixture of 27.9 g. of methyl cis - 1 - methyl - 1,2,3,4 - tetrahydropyrido[3,4-b]indole - 3 - carboxylate and 0.31 g. of the hydrochloride of the same methyl ester. Heating and stirring is continued for 24 hrs., then the reaction mixture is evaporated to dryness. The residue is chromatographed on basic Al_2O_3 column (500 g) previously set in hexane. Elution with benzene gives some starting material, with ethyl acetate/benzene and ethyl acetate gives 6 g. of the desired compound, m.p. 208°C.

Example 31.

cis - 6 - Methyl - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido[3,4-b]indole.

The compound obtained according to Example 30 (5 g.) is hydrogenated with lithium aluminium hydride (4.75 g) in 500 ml of tetrahydrofuran at reflux for 48 hrs. After cooling, the complex is decomposed by the successive addition of water, 10% NaOH and H_2O, filtered and the filtrate, on concentration and crystallization from aqueous tetrahydrofuran gives 4.6 g. of the title compound, m.p. 186—188°C.

Example 32.

2 - γ - (p - Fluorobenzoylpropyl) - 6 - methyl - 1,2,3,4,6,7,12,12a - octahydropyrazino-[1',2':1,6]pyrido[3,4-b]indole.

To a stirred mixture of 10.6 g. of the compound of the foregoing example, 4,25 g. of freshly prepared Na_2CO_3 and 2.4 g. of sodium iodide in 150 ml of dimethylformamide, 14 g. of p-fluoro-γ-chlorobutyrophenone were added and stirring was continued at 80°C for 24 hrs. The reaction mixture was poured on water and extracted with benzene. After evaporation of the solvent in vacuo the residue was crystallised from benzene/hexane. The compound has m.p. 85°C.

Example 33.

2 - (3 - Oxobutyl) - 6 - methyl - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]-pyrido[3,4-b]indole.

Prepared exactly by the procedure described in Example 23. The compound has m.p. 97°C.

Example 34.

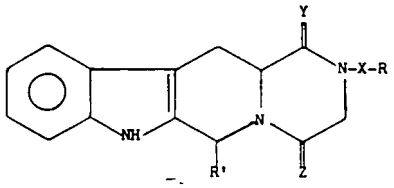
2 - β - (4 - Pyridyl) - ethyl - 6 - methyl - 1,2,3,4,6,7,12,12a - octahydropyrazino-[1',2':1,6]pyrido[3,4-b]indole.

Prepared as described in Example 9 for the analogous compound devoid of substituents at position 6. The m.p. is 216—218°C.

Other preferred compounds of this invention are 1,4 - dioxo - 1,2,3,4,6,7,12,12a-octahydropyrazino[1',2':1,6]pyrido[3,4-b]indole and 2 - [3 - (p - fluorophenyl) - 3-hydroxy] - propyl - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido[3,4-b]-indole.

WHAT WE CLAIM IS:—

1. A compound of the formula



wherein X is a straight od branched alkylene, oxoalkylene or hydroxyalkylene chain; R is hydrogen, lower alkyl, aryl, aryloxy, cyano, carboxy, carbalkoxy, dialkylamino, benzodioxanyl or 4-pyridyl, or XR is hydrogen; R' is hydrogen or lower alkyl; and Y and Z independently represent H_2 or an oxygen atom, with the proviso that when Y represents H_2, Z does not represent an oxygen atom; or a pharmaceutically acceptable acid addition or quaternary ammonium salt thereof.

2. A compound as claimed in claim 1 wherein R' is hydrogen.

3. A compound as claimed in claim 1 wherein R' is lower alkyl.

4. 2 - γ - (p - Fluorobenzoylpropyl) - 1,2,3,4,6,7,12,12a - octahydropyrazino-[1',2':1,6]pyrido[3,4-b] - indole.

5. 2 - Phenylacetyl - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido-[3,4-b] - indole.

6. 1 - Oxo - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido[3,4-b]-indole.

7. 1,4 - Dioxo - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido[3,4-b]-indole.

8. 2 - γ - Benzoylpropyl - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]-pyrido[3,4-b] - indole.

9. 2 - [3 - (p - Fluorophenyl) - 3 - hydroxy] - propyl - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido[3,4-b] - indole.

10. 2 - β - Phenethyl - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido-[3,4-b] - indole.

11. 2 - (2 - Phenyl - 2 - hydroxyethyl) - 1,2,3,4,6,7,12,12a - octahydropyrazino-[1',2':1,6]pyrido[3,4-b] - indole.

12. 2 - (2 - Phenoxy - 2 - hydroxyethyl) - 1,2,3,4,6,7,12,12a - octahydropyrazino-[1',2':1,6]pyrido[3,4-b] - indole.

13. 2 - β - (p - Fluorobenzoylethyl) - 1,2,3,4,6,7,12,12a - octahydropyrazino-[1',2':1,6]pyrido[3,4-b] - indole.

14. 2 - γ - (p - Methoxybenzoylpropyl) - 1,2,3,4,6,7,12,12a - octahydropyrazino-[1',2':1,6]pyrido[3,4-b] - indole.

15. 2 - (3 - Oxobutyl) - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido-[3,4-b] - indole.

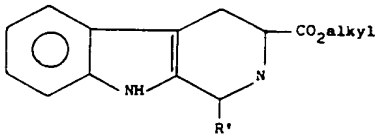
16. 1 - Oxo - 6 - methyl - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]-pyrido[3,4-b] - indole.

17. 6 - Methyl - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido[3,4-b]-indole.

18. 2 - (3 - Oxobutyl) - 6 - methyl - 1,2,3,4,6,7,12,12a - octahydropyrazino-[1',2':1,6]pyrido[3,4-b] - indole.

19. 2 - γ - (p - Fluorobenzoylpropyl) - 6 - methyl - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]pyrido[3,4-b] - indole.

20. A process for the preparation of a compound as claimed in claim 1 wherein XR is hydrogen and Y and Z each represent H_2, which comprises contacting an alkyl 1,2,3,4 - tetrahydro - 9H - pyrido[3,4-b]indole - 3 - carboxylate of the formula



with ethyleneimine in a polar solvent at the boiling temperature of the solvent, and hydrogenating the resulting 1 - oxo - 1,2,3,4,6,7,12,12a - octahydropyrazino[1',2':1,6]-pyrido[3,4-b]indole with lithium aluminium hydride in a nonpolar aprotic solvent at a temperature of from 40 to 100°C.

21. A process for the preparation of a compound as claimed in claim 1 substantially as herein described with reference to the Examples.

22. A compound as claimed in claim 1 when prepared by a process according to claim 20 or claim 21.

23. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 19 and 22, or a pharmaceutically acceptable acid addition or quaternary ammonium salt thereof, in association with a pharmaceutically acceptable diluent or carrier.

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